Actions and Medicinal Use of Snake-Venoms

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When taking up the theme of the actions and the use of snake-venoms we pay tribute to that remarkable personality Constantin Hering (1800-1880) who, while in Surinam (1827-1833), collected, prepared and tested the venom of the "bushmaster" Lachesis muta (then called Trigonocephalus lachesis). After founding, together with Wesselhoeft, the North American Academy of Homeopathic Medicine in Allentown, PA (1835), he published all the data available at that time on *Lachesis, Crotalus horridus, Vipera berus* (then called *V. torva), Vipera Redii and Naja tripudians (Naja naja)*in a booklet (1). Though 120 years of extensive use chiefly of Lachesis and Crotalus have passed, Hering's work is still a main source of our knowledge and use of these venoms. His was the first scientific approach to a subject which has roused the imagination of men from times immemorial.

There is no need here to pursue the many myths on serpents from the days of Adam and Eve through the ages. Not all of them are concerned with venomous snakes, witness the classical statue of Laocoon and his two sons strangled by huge serpents. The more primitive ophidians like the Boidae (e.g., Boa constrictor) use sheer muscular force against their victims. The venomous snakes on which pharmacological interest concentrates are more highly specialized, and significantly so in those morphological and biochemical features which have survival value, viz. feeding on sizeable animals (rodents or even other snakes), and defending themselves against enemies. In view of the but modern medicinal use of snake venoms it is a strange fact that, since Asclepios' times, they have signified the two aspects of the pharmacon as potential poisons or remedies. The snake winding itself around the caduceus and pouring its poison into a recipient vessel has become the symbol for the power of the physician: inimical forces are tamed to heal.

Among the approximately 400 species considered to be venomous, only a few have so far qualified for the inclusion in our materia medica: chiefly *Lachesis muta, Crotalus horridus* and *Naja tripudians (Naja naja)*. Other species of Crotalus (the Central American Cr. durissus terrificus and the South American Cr. terrificus terrificus under the name of Cr. cascavella), Bothrops lanceolatus (B. atrox), three species of the genus Vipera W. berus, V. redii and V. Russellii), Agkistrodon mokeson under the name of Cenchris contortrix, and lastly Elaps corallinus are still of minor importance. These few represent the most poisonous families fairly well.

Though there is no complete conformity with regard to the zoological classification and nomenclature, it is significant that the development of the poison-apparatus has been adopted as a morphological criterion for broad classification, and especially so the development of the formation of teeth or fangs. Those snakes which cannot inoculate venom into their victim by their bite do not come within our scope; they are the Aglyphodonta which have no grooved teeth and the Opistoglyphodonta which possess grooved teeth in the posterior mouth serving as grinders. The two families which concern us as venomous in the stricter sense are the Proteroglyphodonta with two small grooved fangs firmly implanted in the front of the maxilla, comprising the land-snake family of Elapidae (Naja trip. and Elaps corral.) and the Solenoglyphodonta with

the families Crotalidae (genera Crotalus, Agkistrodon, Bothrops, Lachesis) and Viperidae (genus Vipera). The Solenoglyphodonta are the most highly specialized, their two fangs are large, slightly curved and hollow, they inject the poisonous secretion of their supralabial salivary glands, as it were, through a hypodermic needle. In this they are aided by the mobility of the fangs and the jaws, and the synchronized action of several muscles which instantaneously evacuate the salivary glands through the ducts and the tubes of the fangs.

There is no doubt that the counterpart of the morphological evolution is also found on the biochemical level, in the composition of the venoms of the different families and species. The general statement that the venoms of the Elapidae are more neurotoxic, while those of the Crotalidae and Viperidae interfere more strongly with the blood cells and the blood coagulation, is to be considered only as a first approximation. In spite of intense research into the chemical nature of venoms, only some glimpses have as yet been obtained. This is not surprising in view of the fact that dry snake venoms have been found to consist of up to 92 percent of protein. The protein — or at least polypeptide — nature of the active principles is confirmed by a mass of immunological phenomena; they can act as antigens, i.e., they are able to form antibodies when directly injected into the circulating body-fluids of an unrelated species. The immunizing sera thus obtained show a high degree of specificity against that particular venom. From numerous cross-experiments in this field two deductions can be safely made. Firstly, venoms of closely related snakes have similar antigenic composition and, since the antigenic proteins are the active principles, the toxic effects, too, are similar. To some extent such cross-reactions appear even to transcend the class of reptiles altogether, as partial immunization by snake anti-venins against scorpion venoms has been observed. This would indicate that so widely distant types of animals have some active principles of proteinaceous nature in common. A second conclusion to be drawn from pertinent experiments is that each venom is a complex of a number of active principles of antigenic character. At least ten antigens are attributed to the venom of Naja naja (tripudians), the spectacled cobra of India. Between two species of vipers (Viper Russellii and Echis, the saw-scaled viper) at least five cross-reacting antigens have been found. This is, however, not to say that the different antigenic properties are due to so many separate protein-molecules, but rather to distinct active groups on the agglomerate macromolecules. At the present stage of knowledge the various names of these active principles denote merely the kind of effect they have on parts of another organism.

Any foreign protein which gets into the blood-lymph stream by eluding degradation through digestive enzymes constitutes a "poison" and the organism will protect itself against it by a very specific reaction of its globulins, i.e., by the formation of antibodies. In the course of this adaptive process anaphylactic and allergic phenomena are known to occur under certain circumstances. The antigen-antibody reactions represent, in a way, only the spearhead of defensive activities. When in allergic conditions they produce symptoms, these are in the main stereotyped in that they indicate either spasms of involuntary muscles or changes in the permeability of the vessels. According to present theories they are due to the liberation of histamine-like substances from certain cells in the course of the immune-reaction. From our point of view, such syndromes lack distinctiveness, they do not suffice to distinguish the actions of one agent from those of another. For that purpose they have to be supplemented by methodical provings. On the other hand, such allergic syndromes

demonstrate the action of such an "allergens" to be a systemic one. Thus Hering was quite right when he incorporated the symptoms which appeared while he was triturating the venom of Lachesis, into the list of its symptoms. Recently, Stanic (2) has described the allergenic properties of the venom of Vipera ammodytes. When scraping the dry venom from petri dishes he became sensitized by the dust, so that he was seized by sneezing, profuse nasal discharge lasting for hours, and attacks of coughing. He tried to desensitize himself by injecting 0.00001 g. subcut. into the forearm. The dose proved far too strong, since several minutes later urticaria, retrosternal pain and dyspnea appeared; then, through swelling of the tongue, speech became difficult, and finally a heavy asthmatic coughing attack occurred; the forearm gradually got swollen up to the fingers. After a dose of 1:1000000 the reaction was milder and after another one of the same strength very mild. Ten days later he experienced only moderate sneezing from the dust, and coughing with retrosternal oppression. Eight months later all the previous symptoms returned! In order to desensitize himself, he injected 0.000004 g. intradermally and had the same reactions as on the first occasion, but to a somewhat milder degree. Another chemist suffered for months from asthma owing to the dust of the venom in the laboratory, so that he could no longer work in the place.

By such experiences the outworn objection that snake venoms, when given orally, are ineffective stands refuted. To be sure, after 130 years of using the potentized venoms in Homeopathy, there is hardly any need for such corroboration. It is true that the venoms in their concentrated state do not pass the intact mucosa and if disintegrated by digestive enzymes become harmless. But when dispersed as minute particles, and the more thoroughly dispersed the better, they enter the lymph-spaces and produce symptoms. To those engaged in the study of enzymes it is familiar that these proteins develop their specific effects only if sufficiently dispersed. The oral administration of potentized venoms would thus appear to be equivalent to the injection of a highly dispersed solution. Although for the snake it is natural to inject its venom into its prey or enemies through the fangs, it is not particularly biological to inject potencies, nor is it necessary. Only when massive doses are used on general diagnoses, such as epilepsy or carcinoma, does parenteral administration seem justified. The use of snake venoms in these types of disease had had its vogue, but nowadays one hears little of it. More recently Sanders, Akin, and Soret (3) have used neurotoxoids (prepared with hydrogen peroxide as detoxifying agent) of Naja and Crotalus species for checking experimental poliomyelitis in rhesus monkeys. The common affinity of virus and venom for the central nervous system appears to have suggested these experiments. It is of interest to note that only when small amounts of toxoid were used, as late as the fifth day after the intracerebral injection of virus, interference with the infection could be achieved.

As constituents of the saliva of the snakes, the venoms have the function of initiating and facilitating the digestion of animal tissues. The proteins of the venoms must therefore, at least partly, be classified as digestive enzymes, and very powerful enzymes at that. For the snakes devour their victims entire, without troubling to break them up first. No wonder that these strong enzymes are highly toxic for the victims. The horrifying consequences of snake bites have, indeed at all times made a profound impression on men.

If certain proteins of the venoms are distinguished by the epithet "toxin," such as neurotoxin and cardiotoxin, this does not mean that their action is not enzymatic. They may not be digestive enzymes, since their primary function could be to paralyze or kill the prey; but their rapid and strong effects are considered to be due to their interference with vital enzyme-systems of the animal's organism, the proteinaceous "toxins" acting as anti-enzymes. After all, the names are merely provisional, as long as the structural configuration of the agent is unknown; they indicate no more than the main direction of the actions (e.g., neuro-, cardio-, haemo-) of isolated fractions of the whole biological complex of the venom. The names of enzymes, however, acquire a fuller meaning the more precisely their mode of action is understood.

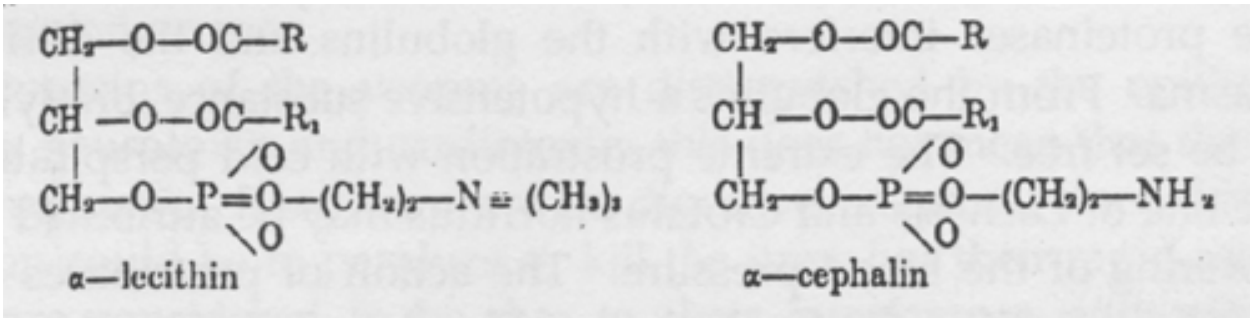
With the progress of biochemical research such terms as proteolysins, cytolysis (including hemolysins and neurocytolysins), coagulins and anticoagulins are replaced by terms denoting the particular enzymes which catalyze the pertinent actions. So far the following enzymes have been recognized in snake venoms: proteinases, which decompose proteins, a 5- nucleotidase which specifically dephosphorylates adenosin-5-phosphate and a l-aminoacid-oxidase; phospholipase A which splits off an unsaturated fatty acid from lecithin and cephalin; hyaluronidase which hydrolyzes the polysaccharide hyaluronic acid; and acetylcholinesterase which hydrolyzes acetylcholine into choline and acetic acid. Of these, the l-aminoacid-oxidase need not be considered here, because no toxic effects are known of this enzyme, nor are they to be expected. Its action seems to be correlated to riboflavin which appears to be present in many snake venoms and to be responsible for their yellow color (4). The 5-nucleotidase may well be responsible for the powerful inhibition of cell-respiration seen from snake venoms, through decomposing the enzyme-apparatus (mitochondria!) of the cells; but nothing definite is known. The acetyl-cholinesterase may play a part, though probably not a decisive one, in the action of some venoms on the neuro-muscular system; it is in this respect suggestive that the enzyme has been found only in venoms of the neurotoxic Elapidae and not in those of the Viperidae.

More than one proteinase is assumed in snake venoms. The principal one appears to be similar to trypsin, but is not identical with it. The decomposition of proteins by these powerful enzymes is apparently the first step in the poisoning process of snake bites. The signs and symptoms at the site of the bite--pain, swelling, blood extravasation and necrosis--are due to this parenteral digestion. Not all the snake venoms cause this local inflammation and necrosis, the Crotalidae and Viperidae more so than the Elapidae (though the bite of Naja causes some pain and swelling). Further the proteinases interfere with the globulins and the fibrinogen of the plasma. From the globulins a hypotensive substance, bradykinin, appears to be set free. The extreme prostration with cold perspiration soon after the bite of Lachesis and Crotalus horridus may be attributed to the sudden lowering of the blood pressure. The action of proteinases on fibrinogen manifests itself in the final stage of blood coagulation, the transformation of fibrinogen into fibrin. This process is generally recognized as proteo-lytic. Like thrombin, the proteinases of snake venoms activate fibrinogen by splitting off a part of the molecule and, in the presence of calcium ions, a rapid polymerization to fibrin then takes place. The structure of the fibrin clot seems, however, not the same as that from thrombin. Most, but not all, of the venoms of Crotalidae and Viperidae promote blood clotting. In some instances the venom proteinase appears to act so rapidly on the fibrinogen that it is decomposed and cannot form a fibrin clot. The venom is then an anti-coagulant. Furthermore, these venoms interfere also with

the preceding stage of blood coagulation, the formation of prothrombin and its conversion to thrombin. This action is, however, probably due mainly to another enzyme of the venoms, viz. the phospholipase A. This will be discussed later. From the quantitative point of view, experimental results with the venom of Vipera aspis are of interest (5). The addition of 1:1000 to 1:5000 concentrations of venom shortened the time of coagulation of recalcified plasma. With concentrations between 1:10000 and 1:50000 the time of coagulation dropped to a minimum level. Further dilutions of the same venom resulted in a new increase of the coagulation time, finally reaching a plateau value which corresponded to the coagulation time observed in the absence of venom. There was thus an optimal effect as to acceleration of plasma-clotting in the range of 10 -5, 10 -6.

The hyaluronidase enzymes found in snake venoms, as in venomous secretions and tissue extracts of many other animals, are not particularly toxic by themselves, but they facilitate the penetration of other toxic substances into the system. They are what used to be called the "spreading factor". By splitting the mucopolysaccharide hyaluronic acid (similar to heparin and chondroitin-sulfuric acid) apparently a normal tissue-protection is removed. The hyaluronidases are antigenic. As the anti-viper sera do not neutralize the spreading effect of the venom of Elapidae, the hyaluronidases of those two series appear to be different.

Phospholipase seems to be the enzyme in snake venoms which has the most deleterious systemic effect. It was first called lecithinase A because it splits a fatty acid off lecithin A, but as it does the same with another phospholipid, cephalin, the name phospholipase A is now preferred. For a better understanding of its action, the formulae of lecithin and cephalin may be recalled:



It will be seen that lecithin is glycerol of which 2 OH-groups are esterified by fatty acids (the second one being unsaturated). The third OH-group is esterified with phosphoric acid and this in turn with choline. Cephalin differs from lecithin only by having colamine in the place of choline. Phospholipase A does not catalyze other phospholipids, but only the two derived from glycerol, lecithin and cephalin. It splits off the unsaturated fatty acid and thereby produces lysolecithin and lysocephalin respectively. It is conceivable that the selective permeability of cell membranes will be thoroughly altered by this. Indeed, the lysophosphatides produced by the enzyme have a strong lytic effect not only on the red blood corpuscles, but also on other cells. The terms of hemolysin and cytolysis can, at the present stage of knowledge and in respect of snake venoms, be replaced by phospholipase A. The enzyme shows antigenic properties and is inhibited by snake venom sera.

Not only erythrocytes but also leukocytes are broken up by phospholipases, and leukopenia and even agranulocytosis may ensue. The phospholipid content of leukocytes on the whole runs parallel to their phagocytic activities. This makes such features of the effects of Crotalidae venoms, especially of Lachesis and Crotalus, as the lack of "pus bonum" and the poor healing tendency of necrotic-hemorrhagic ulcers more easily understood.

Since the cephalin constituent of the blood platelets appears to be the carrier of the enzyme thrombokinase which activates prothrombin to form thrombin, the phospholipases may also interfere with this first stage of blood coagulation. Destruction of thrombokinase would lead to retarded coagulation and a tendency to bleeding, features well-known in the syndrome, especially of Crotalus horridus. The phospholipase content of the venom of Crotalus terrificus terrificus (Cascavella) has been found to be very high (6). In Bothrops species, on the other hand, the phospholipase content was low, their venom is strongly coagulant. This action is generally attributed to proteolytic enzymes, not only on fibrinogen, as mentioned above, but also on prothrombin. According to H. Eagle (7), the Bothrops venoms in extremely low concentrations, convert prothrombin to thrombin and thus set going the coagulation mechanism. The varying proportions of proteinases (acting on fibrinogen and/or on prothrombin) and phospholipases obviously have a profound influence on the syndromes of the different species, especially of Crotalidae and Viperadae. In the Elapidae interference with blood coagulation is much less prominent.

It should be mentioned that lately a useful test for snake (and bee's) venoms has been developed from the action of their phospholipases on egg yolk emulsions, the heat coagulability of which is inhibited. The retardation of the coagulation is measured.

The phospholipases (probably in collaboration with the 5-nucleotidase, as mentioned above, inactivate further physiological enzymes in the tricarbon (or "citric acid") cycle of intermediary cell metabolism, thus interfering with end-oxidation. Particularly the succinodehydrase is known to be inhibited. Such inhibition of dehydrases has been seen from concentrations of snake venom of 1:50 billion (i.e. 10 -13 to 10 -14), while with a concentration of 1:1 million (10-6) inhibition was complete. Crystallized lecithinase A has been allowed to act on mitochondria of liver cells which are known to have a high turnover in phospholipids, and inhibition of the oxidation of succinic acid was then seen. The dehydrases of the so-called cyclophorase system are attached to the mitochondria; the lecithin probably binds the enzymes to the mitochondria. In view of the discussion to follow, it may be recalled that succinodehydrase has a thiol- (SH-) group on which its enzymatic activity apparently depends.

Of special import are the phospholipases for the action of venoms on the nerve system, the neuraxis as well as the medullary sheaths of the peripheral nerves. There the cephalins are known to prevail over the lecithins. When peripheral nerves degenerate, the cephalins are the first to decompose. The neurotoxic principles of snake venoms have generally been termed neurotoxins, but may now be described more precisely as phospholipases, especially cephalinases, decomposing cephalins to lysocephalins. Since Slotta and Fraenkel-Conrat (8) obtained from the venom of Crotalus terrificus terrificus a uniform protein in quadratic, thin, tabular crystals, which they called "crotoxin," it seems established that the neurotoxic activity, too, is due to

phospholipases. The neurotoxic and the (in Crotalus venoms prevailing) hemotoxic actions were found to have the same proportions in the crystalline "crotoxin" as in the crude venom. The fact that crotoxin was free of coagulating principles appears significant. The proportion to which proteolytic enzymes are present in a particular venom may well have a bearing on whether the hemotoxic or the neurotoxic actions of the proteinic enzyme phospholipase predominate; but other directive conditions, as yet unknown, also may play their part. In the Naja naja (tripudians) venom, long recognized as chiefly neurotoxic, Slotta and Fraenkel-Conrat (9) significantly found practically no coagulant nor proteolytic action.

Surprisingly, Slotta and Fraenkel-Conrat did not find in their crotoxin any zinc which, since 1919, has repeatedly been ascertained in snake venoms and was thought to be a constituent of the neurotoxic principle. In view of the affinity of zincum to the nerve system, the presence of this co-catalyst might have presented a clue to the neurotoxic action of the enzyme. It has to be seen whether the more neurotoxic venoms of Naja and the Elapidae generally contain zincum. They were reputed to be particularly rich in the metal.

There is general agreement on the cardinal role which sulfur has in the venom actions, and as a constituent of active atom groupings of the neurotoxic principle in particular. About the configuration of this active group, however, Slotta *et al* (9) and Micheel *et al* (10) held opposite opinions twenty years ago, and up to now the question appears to have remained unsolved. Slotta asserted that all the sulphur of his "crotoxin" as well as of the Naja neurotoxin was present as a cystin-like S-S-bridge, while Micheel interpreted his own tests with Naja venom as showing that the sulfur could not be present in the cystin-like S-S-form, nor a thiolactone or a thiazolidine grouping, both of which had been considered possible. Micheel did not, however, give an alternative solution. In the absence of a better working hypothesis, the present author ventures the following which is amenable to tests: the action group may be a structural analogue of either ax-lipocaic acid (a cyclic disulphide of a low fatty acid, thus containing the S-S- bond) or of the thiazol grouping of thiamine (vitamin B1). Both these compounds are essentially active in the enzymatic process which reduces pyruvate to acetate (by oxidative decarboxylation). Inhibition of this process would then produce syndromes similar to B1-hypovitaminosis or even avitaminosis (Beri-beri). That is to say, the neurotoxic and the cardiotoxic actions of venoms could be traced to the same faulty metabolic process. Furthermore, as a diminished difference in the oxygen contents of arterial and venous blood is a characteristic sign of B1-hypovitaminosis, the familiar "venosity" of Lachesis and other snake venoms could be better understood. In Beri-beri the right auricle and ventricle are known to suffer more than the left ones.

Sarkar (11) has separated an active principle from Naja naja venom which has an affinity to muscle and particularly that of the heart; he has called it "cardiotoxin." Injected intravenously into cats this "cardiotoxin" caused a sharp fall in blood pressure. Anima, Devi and Sarkar (12) observed an increased systole and diastole of the heart when it was per-fused with a solution of Naja venom of a concentration 1:50000 to 1:10000, while with a concentration of 1:400 to 1:300 the heart went into final systolic contracture. In view of the — to us — familiar cardiac syndrome of Naja these finds are noteworthy. The relation of this fraction to the other toxic proteins, though, remains to be clarified.

From the venom of the South Brazilian Crotalus terrificus terrificus another protein has been separated and, on account of its basic properties, has been called "crotamine." Other Crotalus species do not appear to contain crotamine. If that should be confirmed, one would have to make a greater distinction between Crot. horridus and Crot. cascavella than is usually done. The characteristic effect of crotamine is said to be a paralysis of the posterior extremities in mice. As the crotamine has been separated from crotoxin by electrophoresis, it may well be that, in the natural protein complex, the two neurotropic polypeptides are combined.

By and large, these are the relevant facts so far revealed by biochemical analysis of the various venoms. Obviously the relative amounts of the different enzymes in the complex venom of each species will determine the trend of the toxic effects. Though by their nature the snake venoms manifest certain common features when acting on the human organism, contrasts between families are evident, as between Elapidae on the one hand and Crotalidae and Viperidae on the other. With species of the Elapidae, neuro-muscular and cardiac affinities predominate, and the inflammatory, necrotic, hemorrhagic and coagulant signs are practically absent, while with the Crotalidae the latter are pronounced and even more so with the Viperidae. Nor must the time factor in the development of the syndromes be overlooked. Though Naja, for instance, may have hemolytic actions, they are overtaken by those on nerve centers and the heart. Closer examination reveals toxicological differences between genera of the same family and even between species of the same genus. At this point the need for distinctive symptoms and modalities arises, as they are ascertained by systematic provings and then sifted, confirmed and emphasized by experience. These pointers to the "simile" in an individual case have to be elaborated as specifically as possible, they should permit discrimination not only between drugs from different species of snakes, but also from others that may have more or less features in common with snake venoms. For the symptomatology of a patient does not generally lead to the conclusion that the appropriate remedy has to be found among the snake venoms, but the last choice may be, for instance, between*Lachesis* and *Arsenicum album* or between *Naja* and *Spigelia*.

LACHESIS MUTA

It is fortunate that Hering gave his searching mind first and foremost to the venom of the much dreaded "bushmaster" of the South American and Central American tropics. This very aggressive monster excels among the highly specialized family of the rotalidae by its length (up to 3.60 m.) and its large fangs. To judge from the mostly fatal consequences of its bite, Lachesis possesses a full range of strong enzymes; the proteolytic, cytolytic and coagulant ones appear, however, to preponderate over the neurotoxins. The sudden stabbing pain at the site of the bite may extend from the limb to the trunk and become intense, even intolerable, the bitten region becomes edematous and discolored from ecchymoses, and may be covered with blisters; necrosis and even gangrene may set in. A dark oozing hemorrhage is often striking. The lack of purulent discharge shows the low level of defensive reactions in the tissues. The venom spreads so rapidly that general symptoms appear almost immediately. Extreme prostration, cold perspiration, a quickened, weak pulse,

dyspnea, nausea, vomiting and sometimes diarrhea lead to repeated collapse and eventually death.

Such a rapid sequence of events after the bit of Lachesis can manifest only the general trends of the toxic action. The organism has little opportunity to develop its defensive reactivity, the lesions are irreversible. In order to obtain detailed distinctive symptoms, the more transient reactions elicited by suitable preparations and doses of the venom have to be detected and integrated into the picture of drug actions. The gross toxicological effects serve, however, as firm outlines of the picture into which the subtler details have to be fitted. Such a synopsis must depend on present-day physiological knowledge and to some extent the interpretation will be provisional.

Even the gross signs near the point of entry of the venom supply valuable clues for *Lachesis*. Wounds and ulcers are characterized by *poor healing tendency*, no proper suppuration develops, the damaged tissues are not well demarcated, and the *margins are discolored, blue-red*. In a *Lachesis*case the *inflamed regions* of skin or mucosa are often *dark blue or purple* and somewhat swollen by edema. Thin fetid discharges indicate the necrotic and even gangrenous tendency. Ulcers are *sensitive to touch*; the often considerable pains are relieved by warmth. (The frequently asserted aggravation of all *Lachesis* symptoms by warmth is not supported in this and other respects, neither by provings nor by clinical experience.) The more severe cases of varicose ulcers do not seldom show these features and, considering the strong tendency of Lachesis for thrombosis, it is not surprising to find the choice of *Lachesis* vindicated by such gross local signs and symptoms alone. The same may apply in cases of thrombophlebitis, though *Crotalus* may prove superior there.

The mucous membranes of the throat, and in particular the tonsils, are a favorite site for necrotic inflammation which exhibits the characteristics of *Lachesis*. The dark blue-red discoloration, the offensive breath distinguish *Lachesis* well from *Apis* with its pale red acute edema. Sensations of *constriction*, difficulties in swallowing and a feeling of suffocation are only what one would expect in such a case; common to several snake venoms also in non-infectious conditions, they appear accentuated with *Lachesis*. The *high sensitivity to superficial touch*, but not so much to pressure, is a characteristic of *Lachesis* and may lie behind the symptom: *swallowing of liquids is more difficult than of solids*.

The malignant, "septic" character of infectious *Lachesis* cases is underlined by a number of signs and symptoms which are not so much derived from provings as from clinical cases cured by *Lachesis*. The tongue is dry and a shiny red, cracked at the tip, in more severe cases black at the center and red at the tip, swollen, "heavy" and stiff. It is protruded only with difficulty, remains attached to the teeth and trembles. The fever is of the adynamic type. The *discharges are offensive*, the stools in particular are fetid. Skin and sclerae may take on a yellowish tint, but this has to be attributed to increased destruction of the red blood cells rather than to disorders of the liver. It is also due to the hemolytic component if hemorrhages are dark, fluid and do not coagulate easily. On the skin blood extravasations may occur in the form of ecchymoses, purpura or petechiae. In the low fevers of *Lachesis* cold shivers alternate with spells of dry heat; skin and mouth are dry; when sweating does occur, it is felt to be a great relief. This relief from the onset of secretions and discharges, especially

from the onset of the menses, has clinically proved to be a valuable modality, though Lachesis shares it with several other remedies.

In the broad field of cardiovascular disturbances, with their repercussions on respiration and on the sensorium, it appears futile to trace one part to peripheral, another to central origins. For they are interlocked in one functional cycle. What we call "venosity" in the syndrome of Lachesis, as indeed of several other remedies, may be partly due to damaged red blood cells, to a relaxation of the veins from lesions of the intima, venous stasis and thrombotic occurrences, partly to impaired metabolic functions with incomplete end-oxidation, partly to the involvement of the right auricle and ventricle; but either indirectly or primarily the autonomous nerve centers, cardiovascular, respiratory, parasympathetic and sympathetic, will be implicated. That is why we may frequently find *muscular spasms and sensations of constriction* associated with the vasomotor disorders of *Lachesis.* It should be recalled that the snake venoms tend to lower the blood pressure. A tendency to faint from sudden change of position, pallor of the face, some nausea and precordial pain point in this direction. These is also a hypotensive kind of *dizziness with a pale face* alleged to be worse after walking in open air, which contrasts with the modality more frequently encountered in *Lachesis* cases, especially with the congestive headaches of the climacteric: *relief in the open air.* Again this modality is shared by other remedies favored in climacteric troubles, e.g., *Pulsatilla*and *Sepia.* The congestive headaches, often in the form of heat and pulsating on the crown of the head, are *aggravated in the sun*, similarly as with *Glonoin* from which the case for *Lachesis* then has to be distinguished by other symptoms and modalities. *Alternating shivers and heat flushes*are frequent vasomotor symptoms of *Lachesis* without connection with feverish states; another indication for its use in the climacteric. Palpitations and pulsations, a restless anxiety, oppression around the heart, a feeling of constriction in the throat and even suffocation may further mark the spells due to vasomotor imbalance.

The changes from the waking to the sleeping state and from sleep to wakening tend to bring about a marked aggravation of *Lachesis* symptoms, very likely via the autonomic centers of the midbrain. On falling asleep, breathing stops and this causes a sudden start with feeling of suffocation; or an oppression in the precordial region with a fast, weak and arrhythmic pulse may hinder the smooth transition into sleep. The peculiar constriction in the throat, the feeling of a tight collar around the throat, too, may come in. Even more marked is the aggravation of most symptoms on awakening from sleep; *"the patient sleeps into aggravation"* is the usual term for this modality of *Lachesis*. The same modality is, however, found not only with the venoms of other snakes, but also with those of other animals, such as *Apis* and *Bufo.* In some cases the starts when falling asleep (even more characteristic for *Digitalis* than *Lachesis*) may be early signs of insufficiency from anoxemia or even structural lesions of the heart muscle. (In true angina pectoris *Latrodectus mactans* has proved superior, when the icy coldness of the extremities during the attacks indicated the spider venom.)

The heightened surface-sensitivity to touch and the spasmodic tendencies, already alluded to above, are of general significance in the Lachesis syndrome. They manifest the lowered threshold in the sensory motor reflex mechanism. The region of the throat and larynx appear to be peculiarly sensitive and prone to respond with sensations of *constriction*. (The snake does not seem to suffer from it when it swallows a rabbit entire!) The feeling of constriction is also noted in the stomach region and around the

abdomen which may be distended from portal stagnation. In the lower abdomen the sensation is supposed to occur frequently in connection with inflammations and cysts of the ovary, with preference to the left one. The latter detail, though derived merely from clinical observations, has proved useful for discriminating against *Apis* which appears to affect rather the right ovary. It would be futile to look for an explanation. The assertion that the throat syndrome of *Lachesis* is left-sided or starts on the left and goes to the right, cannot be supported in the experience of the author. To some extent the predilection for the left side is accounted for by the heart symptoms of *Lachesis*. Judging from the provings, the left-sided symptoms surpass the right-sided ones chiefly in the neuromuscular sphere. Paretic conditions, numbness and other parasthesias are recorded almost exclusively for the left side. Thus on the whole the old assertion that *Lachesis* is one of the *left-sided* remedies can be upheld.

The sensitivity io touch may go to such extremes that even the *contact of tight clothes* and that of the bed-clothes on the abdomen *is ill tolerated* and avoided. Though pressure is generally not so unpleasant as slight touch, a tight collar or waist-band are aggravating. In the motor sphere, symptoms such as tremulous weakness and a certain lameness of the left side are not particularly characteristic. If in paralyses from apoplectic insults *Lachesis* be called for, it is on the strength of peculiar symptoms and modalities. The use of *Lachesis* in epileptic conditions seems, however, to have been unduly neglected of late. In the early days already Hering and Gross reported good results in clear cases of epilepsy, and the present writer remembers having seen benefit from *Lachesis* in a few cases, especially of "petit mal". Indeed, a number of the symptoms of *Lachesis*point strongly in this direction. The fits of vertigo show epileptoid traits: viz. staggering, threatening to fall to the floor and as if to lose consciousness; marked failure of memory, does not remember what he has been told just before, loses the connection in speaking, makes mistakes in writing, sense of time is deranged. It is not surprising that the indiscriminate use of snake venoms merely on the diagnostic indication "epilepsy" has been abandoned, but there are good grounds for a selective use of *Lachesis* in individual cases. It is in these cerebral disorders that the often repeated, but scarcely verified modality "complaints recur in spring" may find some justification; it might be related to the better substantiated modality, mainly for congestive symptoms of the head, *"aggravation from exposure to sun"*. A similar recurrence and increase of fits is known in the brain-injured, and there, too, the first piercing rays of the sun may be held responsible for the aggravation.

Finally, the actions of *Lachesis* on men culminate in a wealth of diverse psychic symptoms. They are well brought out by Hering in the booklet mentioned above. In his annotations he even expresses some surprisingly modern views on the emotional determination of psychic disorders. The two main constitutional trends, the cyclothymic and the schizothymic, are well represented in the symptomatology of *Lachesis*. A submanic state was experienced by Hering himself while triturating the venom. The mental activities, particularly the imagination, were stirred up to a kind of ecstasy. *Loquacity*, a good characteristic of *Lachesis*, goes to the brink of incoherence and "flight of ideas". The contrasting depressive phase of sadness, anxiety, and fears is also brought out, but apart from the general modality that it is worse after sleep and in the morning, it has no distinctive features. In the schizothymic sphere, two phases are also apparent: an emotional indifference and a paranoid state. The symptoms of the latter, *suspicion, jealousy* and a certain supercilious and quarrelsome behavior, have proved the more characteristic and useful clues to *Lachesis*. It is said

that grief, disappointment and mental anguish are at the root of the psychic symptoms of *Lachesis,* but that is too common to be of distinctive value. If the psychic abnormalities develop in the climacteric, it is one more reason to consider *Lachesis* as the remedy.

To sum up:

LACHESIS MUTA
(Reptilia; Ophidia; Solenoglyphodonta; Crotalidae)

1. ACTION ON BLOOD PLASMA, BLOOD CORPUSCLES, CAPILLARIES, VEINS

Inflammations and ulcers on skin or mucosa discolored dark blue and purple; wounds and ulcers with blue-red margins.

Impaired reactivity and demarcation (Leukopenia and agranulocytosis).

Affected parts highly sensitive to touch.

Thrombosis, embolism, thrombophlebitis.

Necrotic-gangrenous tendency.

Blood disintegrates easily, is fluid, dark, does not coagulate properly.

Yellowish skin and sclerae, hematogenic icterus.

Ecchymoses, purpura, petechiae.

In infectious conditions: adynamic fever, tongue dry, shiny red, trembling, protruded only with difficulty; dry skin, perspiration relieving.

Secretions offensive; decomposed, fetid stools.

Anoxemia of parts and venous stasis, "venosity".

Better from onset of discharges and hemorrhages, e.g., menses.

2. CARDIOVASCULAR AND VASOMOTOR EFFECTS

Hypotension, dizziness with pale face, tendency to faint.

Congestive headaches, relieved in open air, aggravated in the sun, cold extremities with head hot, cold shivers alternate with flushes of heat (climacteric!). Palpitations with anxiety and oppression.

Heat, pulsating, pressure especially on top of head, worse from sun. Spasmodic oppression in precordial region, pulse fast, weak, sometimes irregular.

On going to sleep, breathing stops, sudden start, with feeling of suffocation.

Sleeps into aggravation.

Dry throat, feeling of suffocation especially if throat is touched externally.

Swallowing of liquids more difficult than of solid food; constraint to empty swallowing.

Strong feeling of constriction in the throat; collar-sensation.

Very sensitive to the touch of clothes, especially neck and abdomen; tight band also ill tolerated. Distended abdomen.

Left side more susceptible, e.g., left ovary.

3. ACTIONS ON NERVE SYSTEM (NEUROMUSCULAR, SENSORIUM, PSYCHE)

Hyperesthesia and hyperreflexia, see above: slight touch provokes spasms.

Trembling weakness bordering on paresis (left side preferably affected).

Epileptoid: vertigo, cannot recall recent happenings, loses connection when talking, makes mistakes in writing, deranged sense of time.

Submanic state: ecstasy, loquacity, "flight of ideas".

Depressive phase: sadness, anxiety, fears worse after sleep, in the morning.

Paranoid state: suspicious, jealous, supercilious, quarrelsome.

Emotional indifference (in another phase).

MODALITIES

Worse after sleep.

Surface-sensitivity to touch, provoking spasm and constriction (especially throat, stomach, abdominal region); cannot bear anything tight there.

Congestive symptoms worse from sun, better in fresh, cool air.

Relief from onset of discharges.

Predominantly left-sided.

DOSAGE (Author's)

12x twice a day, 30x and 30, single doses at varying intervals.

CROTALUS

The two species of the genus Crotalus which have been introduced into our materia medica, Crotalus horridus by Hering and Crotalus cascavella by Mure, should be well distinguished from each other. Unfortunately, we cannot be sure whether the extensive symptomatology of Crotalus horridus has been obtained solely from that species, the "timber rattler" of the eastern and central states of the USA, for in other parts of North America different, though closely related species are encountered. Moreover, it seems that Crotalus durissus terrificus of Central America has not always been distinguished from Crotalus horridus. Mure's Crotalus cascavella (from the Latin-American name "cascabel" or "cascavel") was almost certainly what nowadays is known as Crotalus terrificus terrificus, found in Brazil and Argentina. (As Crotalus durissus terrificus in Central America is also called cascabel, further confusion may arise; but the latter species need not concern us here.)

As mentioned before, the venoms of Crotalus horridus and Crotalus terrificus terrificus show marked differences in their composition. The "crotamine" separated from the proteins of Crotalus terrificus terrificus (Cascavella) is not found in the venom of Crotalus horridus. This may explain why the bite of Crotalus terrificus terrificus has less localized effects, less pain, inflammation and necrosis, but is more lethal through protracted action on cell respiration and nerve centers than that of Crotalus horridus. The latter acts more rapidly and appears to deploy foremost proteolytic and hemolytic properties. Among the numerous cases reported of bites by the North American rattlesnakes remarkably many have recovered, though the condition appeared most alarming. Whether this was due to the much advocated and liberally dispensed whisky is another matter.

To judge from the sequelae of the bite, the venom of Crotalus horridus acts foremost on the walls of the blood and lymph vessels. Intense edema spreads rapidly and, in the wake of it, bleeding into the tissues occurs, so that the whole spectrum of discoloration from black, purple, blue to yellow may show itself. Apparently from the massive destruction of red blood cells, skin and sclerae become icteric. Bleeding from any orifice of the body, even from ears and eyes, has been seen. The blood is dark and remains fluid. The venom inhibits coagulation, whether in the fibrinogen-fibrin or in the prothrombin-thrombin phase or in both, cannot yet be said. It has further to be considered that the proteolytic and hemolytic enzymes of the venom cannot be termed simply as "anticoagulants," but in different proportions, especially in low concentrations of the proteolysins, they could act as "coagulants" as well. The immediate lesion of capillary walls by the venom of Crotalus was well demonstrated by the experiments of Hayward (*Mat. Med. Physiol. and Applied, I,* cited from *Cyclop. of Drug. Pathogen.*, II pp. 418 and 420). He applied the venom, dissolved in glycerine, to a small spot, from which the cuticle had been scraped off; immediately blood began to flow excessively. The consequent symptoms of his inoculation experiments, too, are noteworthy, as they supplement those observed from bites on the one hand, and in provings with potencies on the other.

The *tendency to hemorrhages* is an outstanding feature of *Crotalus horridus*. In this respect it exceeds *Lachesis* significantly, and from the practical point of view it has

proved useful in differentiating between the two remedies, otherwise so closely related. A hundred years ago, inoculations with Crotalus venom had been used extensively as prophylactic for yellow fever, the hemorrhagic signs, black vomits (like "coffee grounds"), black fetid stools and the jaundice apparently pointing to a similarity in the morbid processes. It is difficult enough anyhow to assess the prophylacticvalue of a remedy, but even more so in respect of diseases of which one has only knowledge from books. There is, fortunately, hardly any opportunity left for testing the curative value of *Crotalus* in yellow fever. All kinds of hemorrhagic diatheses may, however, come into the orbit of *Crotalus*, though the evidence in a particular case must decide whether or not other remedies, e.g., *Phosphorus,* are more suitable. In purpura haemorrhagica and in haemophilic extravasations *Crotalus* is among those remedies which have to be considered foremost. Intra-ocular bleeding in particular is adduced for *Crotalus*. Clinically some good results have been seen even in bleeding carcinomata of the tongue and of the stomach with "coffee ground" vomits and thin, black, fetid stools, though no more than palliation is to be expected in such cases; further, in infectious conditions which, by severe disorganization of the blood, extravasations, adynamic remittent fever with muttering delirium show a "septic" character. As with *Lachesis*, the site of origin is frequently found in the fauces, but carbuncles with blue-black and yellow discoloration are also cited. The ulcers with their unhealthy granulations and discolored margins are similar to those described for *Lachesis*.

In thrombotic processes *Crotalus,* in contrast to *Lachesis*, is hardly ever mentioned, but unjustly so, it seems. At first sight the strong anticoagulant action of the *Crotalus* venom may be taken to vindicate a heparin-like use of the venom rather than a homeopathic one. It has, however, to be kept in mind that the formation of thrombi, and thrombophlebitis in particular, constitute processes very different from extravasal coagulation. They involve a lesion of the intima of the vessel first and subsequently an agglutination of platelets. Both are well within the potential actions of*Crotalus*. It is true that the provings in this direction have not brought out much more than cramp-like pains, especially in the legs. The appended case-reports of O. E. Manasse are all the more welcome to show that in thrombophlebitis *Crotalus* can be just as effective as *Lachesis*. The cramp-like pains in the legs in such cases are so as to make standing almost impossible and become worse on stretching.

In the cardiovascular and vasomotor sphere *Crotalus horridus* has so much in common with Lachesis that only certain differences need to be pointed out here. Heart symptoms are less prominent with *Crotalus horridus,* in particular the spasmodic, oppressive pains have not been recorded. Hence there is no indication for its use in angina pectoris. Anxious oppression, shaky feeling about the heart, sudden giddiness and prostration even to a kind of somnolence are, as with *Lachesis*, indicative of a hypotensive state. Congestion to the head and cold extremities are likewise a feature of *Crotalus horridus*, but the alternative shiverings and hot flushes are less marked. In the climacteric *Crotalus* cannot compare with *Lachesis*. The headaches of *Crotalus* are often severe and one-sided, mostly frontal, and as they are frequently accompanied by nausea and even vomiting, *Crotalus* may have equal claim with Lachesis in migraine, though the latter is usually preferred. The assertion that *Crotalus* has a predilection for the right side has, since Hering, been copied faithfully again and again, but it is not borne out by the provings where the headaches appear at least as much on the left as on the right side. In the author's experience this modality has no

selective value. The headaches of *Crotalus* are relieved in the open air, like those of *Lachesis*: but the aggravation in the sun is not mentioned for *Crotalus*. The aggravation from sleep should be less emphasized for *Crotalus* as the provings offer some evidence to the contrary, i.e., disappearance of symptoms after a good night's sleep. *"Drowsiness, but cannot sleep"* is more characteristic for *Crotalus*, not so much the *"starts with suffocation"* found with *Lachesis*.

A feeling of *constriction in the throat* has been noted with *Crotalus* too, and that without signs of the mucosa being affected. *Difficulties in swallowing* are said to *arise from solids rather than from liquids*, in contrast to *Lachesis*. The sensitivity to touch is less emphasized with *Crotalus* than it is with *Lachesis* tight pressure around the neck and the hypochondria are ill tolerated in the case of *Crotalus* like in that of *Lachesis*.

Hyperreflexia is less marked than with *Lachesis.* There is also nothing known of *Crotalus* being used in epileptoid conditions, though clouded perception, forgetful behavior, mistakes in writing, incoherence in conversation have been recorded with *Crotalus* as well. As there is no evidence of *Crotalus* acting directly on nerve centers, it may be thought that these symptoms of mental confusion are due to congestion of the brain. Post mortem findings in lethal cases of *Crotalus* bite tend to support such a view.

In such grave derangements of the organism as *Crotalus* can bring about it is no wonder that depressive symptoms, anxiety and fear of death are observed, but they are not distinctive. A certain sentimentality has been recorded in the provings of *Crotalus,* but this, too, does not seem to have any peculiar significance in determining the choice of *Crotalus* as a remedy. The paranoid symptoms described for *Lachesis* are absent from the syndrome of *Crotalus horridus*.

In cases of snake bite, particularly of Crotalus and Vipera, it has been noted that local signs reappear for years at periodic intervals. Old records have it that this happens annually at the time of the accident, but in a well-authenticated case of rattlesnake bite (Piffard, *Amer. Med. Recorder*, Jan. 1875, cited *Cycl. of Drug Pathog.*, II, 429) local signs of inflammation with eruption of small vesicles recurred at regular three-monthly intervals over at least six years. This and other instances of chronic ailing after recovery from the acute poisoning go to show that the venom can have a long-lasting effect with periodical exacerbations. For the often repeated assertion "aggravation in spring" there is, however, hardly any support. Even the modality "aggravation of complaints at the onset of warm weather" is not supported by the provings and needs confirmation before it can be accepted as characteristic for *Crotalus.* Whether the alleged indication for *Crotalus,* "old wounds and ulcers reopen," is merely an inference from the just mentioned periodical recurrence of symptoms or is of clinical significance remains to be seen.

CROTALUS CASCAVELLA

Crotalus cascavella has more neurotoxic properties than Crotalus horridus. Local symptoms and signs from the bite of Crotalus terrificus terrificus (Cascavella) are less apparent. The sequelae do not develop so rapidly as with Crotalus horridus, but are

rather more insidious. This is shown, for instance, by an impairment of the visual function, even blindness, lasting from minutes to several days, which may persist after the patient has recovered. In Mure's proving this is reflected by "the sight is affected" and "a dazzling blue light before the eyes." The auditory system, too, appears to be affected, for the prover experienced deafness (on the second day) and recorded "very deaf (after a month)." In the later stages of poisoning by the venom of Crotalus terrificus terrificus, muscular pareses and paralyses appear and impair locomotion. Of this action the provings revealed only "weariness of the arms and legs," "muscular prostration, trembling of all the limbs" and some other, even less definite, symptoms. Mure's provings are, however, no more than a good beginning, as they are obtained from too few provers. Like all other neurotoxic venoms, that of the Crotalus cascavella increasingly impedes the respiration up to the fatal end; whether through action on the medullary centers or on the respiratory muscles, or both, is not yet clear. Impeded respiration, oppression of breathing, suffocative feeling are noted in the provings, but such symptoms could arise from blood disorganization or interference with cell metabolism as well. From what we know so far of Crotalus cascavella, it appears closer to Lachesis than to Crotalus horridus, and possibly even exceeds Lachesis in neurotoxic properties.

DOSAGE
Author's experience of *Crotalus horridus* almost exclusively with the 6th (12x) potency.

BOTHROPS LANCEOLATUS

The genus Bothrops is represented by some forty species in tropical America. The name Bothrops lanceolatus refers to the 'fer-de-lance' of the isle of Martinique, but it is doubtful whether this species differs from Bothrops atrox. There are no provings of the venom. What little use has been made of Bothrops in homeopathy can therefore not have been very discriminative. C. H. Ozanam (*L'art med*. 19, 116, cited F. T. Allen's Encyclop., II, 210) has, however, reported on a number of cases of Bothrops bite which fill in many details in the literature available on this special subject.

The effects of Bothrops venom, chiefly on the blood and blood-vessels, are formidable. The first stages remind strongly of Crotalus horridus. Under intense pain immediate edema spreads rapidly, followed by serosanguinous infiltration of the subcutaneous tissue, ecchymoses and hemorrhage. Bleeding occurs from the engorged mucous membranes and skin, the throat is parched, thirst intense. Complete exhaustion may lead to the fatal end. Where death does not supervene, suppuration, necrosis, gangrene and sloughing of tissues to the bones may lead to gross mutilation. In this the course of events appears to differ from that of Crotalus; possibly the much higher coagulating power of Bothrops venom, thus its tendency to thrombotic and embolic processes, has something to do with it.

While some of the paretic conditions described as consequences of Bothrops bite are undoubtedly due to thrombo-embolic processes, for instance a hemiplegia of the right side and inability to articulate without there being any affection of the tongue, it is not sure whether the same is true for other lesions within the neuraxis. From experiments there is less evidence of a neurotoxic action from Bothrops than from Crotalus terrifi-

cus terrificus, but this assertion may not be final. Blindness both immediately after the bite of Bothrops and a more persistent one have been noted, and in particular a "blindness" during daytime only; the latter may well have been due to bleeding in the fovea centralis retinae and the other amaurotic occurrences to embolism at other sites in the optical apparatus. The same may apply to the observed paralysis of one arm or one leg; a direct action of Bothrops venom on nerve cells cannot, however, be excluded.

In the absence of provings, *Bothrops* has to be chosen on the indication of gross pathological signs which are, however, insufficient to distinguish it from other Crotalidae. The author has tried *Bothrops* 12*x* in several cases of persistent aphasia after cerebral apoplexia. Though some improvement was seen in one or two patients, the results were not conclusive.

CENCHRIS CONTORTRIX (Ancistrodon Mokeson)

Agkistrodon (or Ancistrodon) is another genus of the Crotalidae. The species introduced into homeopathic materia medica is Ancistrodon Mokeson whose habitat is almost the same as that of Crotalus horridus, namely the eastern and central parts of the USA. There the common name of this mocasin snake is "copperhead" and, as it has a bad reputation for its vicious nature, "copperhead" had become a personal invective.

There are so far hardly any grounds for the homeopathic use of *Cenchris*; the author has no experience of it. Cases of persons bitten by the copperhead are not of sufficiently precise and detailed description to permit the syndrome to be distinguished from that of *Crotalus horridus* or *Lachesis*. Experimental analysis has shown the venom to be highly proteolytic. It retards or inhibits blood coagulation, is, at least in massive doses, hemolytic and causes hemorrhages; a rapid fall in blood pressure accounts for the extreme prostration, fainting and collapse.

A proving of *Cenchris* is found in Kent, *New Remedies* (Chicago, 1926, p.88). Unfortunately the long list of symptoms from five provers, three female and two male, is open to severe criticisms. It is hardly feasible to attribute all the symptoms noted by the provers within three weeks to the one dose of the 6th or 30th or 10m potency. Furthermore, it looks as if the provers knew what they had been given and were even acquainted with the *Lachesis* syndrome. There are too many symptoms phrased in almost identical terms as they are found in any essay on *Lachesis*: sensitive to clothing about the body and neck, tight clothing unbearable, suspicious of everybody, stops breathing on going to sleep, etc. It would be premature to emphasize the few differences from Lachesis in this proving of *Cenchris*, such as "most symptoms are better in the morning." More systematic provings and confirmation by clinical use are needed before a dependable drug picture of *Cenchris* can be drawn.

VIPERA

In the older classification the name "Viperidae" applies to all Solenoglyphodonta, comprising all the "vipers." The pitless vipers of Europe, Africa and Asia would then

have to be separated form the American pit vipers or Crotalidae as "Viperinae." (The "pit" present in the Crotalidae and absent in the Viperinae is a cavity on each side of the head of the snake, between the eye and the nostril.) The genus Vipera is represented by Vipera berus (the common adder or German "Kreuzotter") and the similar Southern species Vipera redii. The use of the Indian "daboia," Vipera Russellii, has been advocated by Le Hunte Cooper on the ground that its venom interferes most strongly with blood coagulation. Of all these species numerous cases of the severe consequences of their bite have been recorded, but no provings on healthy persons. There are thus only a few clinical features indicating Vipera in preference to one of the Crotalidae.

The signs and symptoms of persons bitten by a species of Vipera accord with the analytic finding that proteolytic enzymes predominate in the venom. Interference with the process of coagulation is marked, but it cannot be stated in terms of either promoting or inhibiting the clotting of blood, since that depends on the concentration of the enzyme and possibly other circumstances, and furthermore, the clots formed by the venom are not of the same structure and consistency as normal ones. A tendency to bleeding into the tissues is conspicuous and indicates an enhanced permeability of the vessels, especially the veins, through lesions of their walls. The extensive extravasations could account for the jaundiced hue of skin and sclerae mentioned in some instances. Hemolysis does not appear to play a prominent part, certainly there is no evidence of the liver being particularly involved. Some paretic and paralytic signs are reported in cases of Vipera bite, suggesting the presence of a neurotoxic component in the venom, but this can be only of minor significance in view of the overwhelming hemotoxic actions.

Very rapid and strong reactions of the tissues around the site of the bite are to be expected from this kind of venom. With Vipera the hardness of the intense and fast-spreading swelling has been noted, pressure by a finger makes hardly any "pitting" impression. The swelling is painful to touch. Discolored stripes follow the course of the cutaneous veins, a tense bluish-red swelling causes pain as if it would burst. Besides extensive ecchymoses, spots of purpura hemorrhagica may be seen. The systemic syndrome follows the pattern known from other hemotoxic venoms: fall of blood pressure, fainting, rapid and thread-like pulse, nausea, vomiting and frequent, sometimes bloody and involuntary stools, collapse, and in fatal cases, coma. Albuminuria and hematuria, too, frequently seem to contribute to grave exhaustion through the depletion of water and proteins in the circulating fluids.

In the absence of provings the homeopathic use of *Vipera* is restricted mainly to a venous syndrome confirmed by clinical experience: *unbearable pains in the extremities when they are hanging down, as though they were going to burst;* the patient must keep the affected extremity in a raised position. In the cases where the author used *Vipera berus 12x* with success the leg swelled instantly and grew purple on hanging down, relief being felt in horizontal position of the leg and in walking. One patient who showed the syndrome and the result of the medication strikingly was a diabetic.

Chronic cachexia after the bite of Viperia has been recorded and an annual recurrence of local and systemic symptoms at the onset of hot weather and at the time of the year when the bite occurred has been reported in too many instances to be wholly

overlooked. It has to be seen whether this periodicity can serve as a clue to the use of *Vipera* in chronic ailments.

NAJA

The spectacled cobra of India, *Naja naja* (tripudians) is to us the main representative of the Elapidae, a family of the Proteroglyphodonta with small longitudinally grooved fangs. As accidents from the bite of the cobra go into many thousands a year, there is an abundance of records, more or less reliable, from which to abstract the characteristic features. The recently improved knowledge of the components of the venom serves as a helpful criterion. The provings done a hundred years ago with very low potencies have supplemented some useful details (Stokes, *Br. Jour. of Hom*. 11, 95, 1853; Russell, ibid., 593 and 12, 244; Stokes, *Monthl. Hom. Review*, 3, 162, 1859, cited *Cycl. of Drug Pathog.*, Vol. III, 328). Further, more methodical provings, using a wider range of potencies, seem highly desirable, however. For, judging from the homeopathic literature, this potent drug has been used comparatively seldom so far, apparently through lack of precise distinctive modalities.

It has long been recognized that the venom of Naja (as of other Elapidae) contains a very potent neurotoxic principle acting on the autonomic centers of the medulla. It is not yet certain whether its hemolytic principle is altogether separable from the neurotoxic. The acetyl-cholinesterase present in the venom of Elapidae may well be a co-factor in their action on muscles. The "cardiotoxin" recently isolated from Naja venom lends new weight to the well-established homeopathic use of Naja in heart disorders. Failing of heart and respiratory functions complement each other in the main syndrome. In some cases of cobra bite local symptoms--swelling, mottled appearance, necrotic ulceration and even gangrene--have been reported, such as is usually associated with proteolytic actions of venoms. Generally these local effects on tissues and on blood coagulation are, however, much less in evidence than from the venoms of Crotalidae and Viperidae.

The bite of the cobra causes a sharp pain. The extent of swelling varies considerably. A peculiar numbness of the limb indicates an early involvement of sensory nerves. Soon lassitude, drowsiness and confusion set in, sometimes swooning fits; receding consciousness may lead to outright coma. Difficulties in breathing are pronounced. Paralysis of the tongue and of laryngeal muscles may complicate the dyspnea. The *heart action is accelerated*, may be *irregular in rhythm and unequal in force,* the pulse becomes threadlike. In some cases dribbling of saliva and mucus and foaming at the mouth is seen; in others various signs of paresis develop, the eyelids droop, deglutition is impeded, speech becomes labored, limbsare paralyzed and control of sphincters is lost. In the later stages even trismus, locked jaws and convulsions may occur. Death is then due to respiratory paralysis.

The cardiac syndrome is in the center of the picture of *Naja*, but almost invariably it is associated with symptoms from the respiratory tract and in particular the larynx. It might be inferred that the right heart is more and earlier affected than the left ventricle. In the circulatory sphere *coldness of the body and extremities prevail* with

a *desire for warmth*; the severe *headaches,* often of the migraine type, appear to be *congestive*, they are *relieved in open air*. The pain is mainly in the *forehead* or *temples*, more often left-sided, and as a prover recorded, *attended by fluttering of the heart.* The provings have added some details to the heart syndrome as described in cases of poisoning: *unusual beating of the heart, audible to himself;* feeling of *"lowness" about the heart*, as of something wanting about the precordia; pressive pains in the left pectoral region; *pain at the heart, extending through to the left scapula*, and pain between the shoulders; sudden *sense of choking*, a sort of *grasping at throat; gasping for breath*, with several deep-drawn inspirations; constriction of chest, ending in mucous expectoration; uneasy dryness in fauces, *constriction and irritation of larynx,* sharpish prick in larynx causing cough; hoarseness; tightness of larynx; *constriction, pressure and gagging in throat;* great dryness of mouth and throat. Cases of failing heart, at various stages and of different etiology, somewhere the bundle of His seemed specially affected, appear to have been benefitted by *Naja,* in the experience of the author (12*x*), particularly in post-infectious cases of children. A *tendency to collapse* would strengthen the call of *Naja*. Aggravation from movement and exercise is only what one would expect in these myocarditic conditions. The modality "cannot lie on the left side" is found in most drugs affecting the heart, but for *Naja* its significance has to be reconsidered in view of the observation of a prover that pain and breathing were much relieved by lying on the affected side (in this instance the right side).

It has been claimed for *Naja* that it has a place in angina pectoris and coronary thrombosis similar to that of *Lachesis*. The claim has been based on the syndrome: cardiac pains go to the nape, or into the left shoulder and left arm; they are accompanied by anxiety and fear of death. This syndrome cannot be traced, however, in the provings, and so far seems insufficiently corroborated by experience.

The association of heart symptoms with *left-sided headaches of migraine type* suggests that *Naja* disturbs the vagus-sympathetic balance, before it affects the heart muscle itself. The symptoms then are so similar to those of *Spigelia anthelmia* that the choice may become difficult. With both, the left frontal eminence and temple are seats of predilection and the eye is frequently involved; the pains are violent and throbbing, often accompanied by nausea, sometimes by vomiting, they may extend to the back of the head and are worse from movement. For *Naja* a shooting pain from one temple to the other is mentioned and it is perhaps significant that the *headaches come on during the night* and disturb sleeping, and that they are *particularly bad on awaking*; they are *aggravated by motion and exertion, relieved in open air.*

The psychic background of the *Naja* syndrome is well brought out by the provings: sadness and irresolution, the mind broods over imaginary troubles, dull spirits, head heavy, with dull, confused mental state, a feeling of depression; feeling prostrate and miserable.

In view of the recent animal experiments with *Naja* venom on poliomyelitis it may be mentioned that another species of the Elapidae, Bungarus (coeruleus?), has been recommended for this viral infection.

ELAPS CORALLINUS

We are not yet in a position to give a concise and reliable account of the actions of the Brazilian coral snake, Elaps corallinus. In the first place no detailed descriptions of the sequels of its bite are available. Nor has an analysis of the venom been made known which would permit us to ascertain the characteristic trends from the nature of the active components. Being a species of the Elapidae, Elaps is supposed to contain in its venom mainly neurotoxic and hemolytic principles. The provings of Mure (*Pathog. bresil,* loc.cit.) on two persons, and Lippe's (*Allg. Hom. Ztg.*, 61, 28, 1860) on one lady only are too scanty for drawing a consistent picture of *Elaps*. The expectation of Lippe that *Elaps* would be helpful in various heart disorders is hardly substantiated by conspicuous symptoms in the provings, nor is it confirmed by experience.

So far as the meager evidence goes, the vasomotor syndrome is similar to that of *Naja*: severe headache mainly in the forehead (aggravation during the night and on awakening is mentioned only once). All the blood seems to be congested in the head, the feet are ice-cold and the (right) hand blue and as if paralyzed, benumbed and unsteady. Ears and eyes appear particularly involved: deafness, buzzing and crackling in the ear and vertigo with tendency to fall forward; a grey veil or a cloud, or fiery and colored spots before the eyes, unsteady vision (letters run together when reading), strong aversion to light and even transient blindness. Of the mental symptoms "excessive horror of rain" and "hears what is said without understanding it" may be mentioned with all due reservation. The solitary symptom of one prover "fruits and cold drinks lie on the stomach like ice" seems to have been over-emphasized. Constrictive sensations, familiar from many other snake venoms, are reported from the esophagus and the sphincter ani and vesicae in the provings of *Elaps.*

To judge from the provings, *Elaps* has a greater tendency to hemorrhages than *Naja*. The black color of the blood, from the respiratory tract on coughing, from the rectum and from the uterus between the menstrual periods, is peculiar; bright ("arterial") blood from the nose and ears is, however, also recorded. Much more information is wanted before the significance of these observations can be assessed. Likewise some data in the provings, hinting at chronic inflammation of mucous membranes of nose and ear, should be regarded with caution: bad smell from the nose and stoppage of both nostrils; discharge of a yellowish-green liquid from the ear. It would be rash to assert the usefulness of *Elaps* in ozena from the former and in otitis media from the latter date in the provings.

From the foregoing survey it will be obvious to what different degrees the drug pictures of the snake venoms have been elaborated up to the present juncture. Any survey of this kind is bound to be *pro tempore* and to expose the gaps of our knowledge and experience. On the other hand, this chapter of our materia medics stands to gain in perspicuity, when seen in the broader context with the venoms of other classes of animals, such as spiders, scorpions and insects.

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